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Ocular malformations, postaxial polydactyly, and delayed intramembranous ossification: a new autosomal dominant condition

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EDITOR—Microphthalmia and related ocular abnormalities are a common component of many multiple congenital anomaly (MCA) syndromes.[1] Microphthalmia has a birth prevalence of between 1 and 1.5 per 10 000 and unilaterality is reported in a half of those cases associated with other anomalies.[2 3] Of the many MCA syndromes associated with microphthalmia, several include skeletal defects and distal limb anomalies, including polydactyly, syndactyly, and radial aplasia. However, while many genetic conditions include both ocular and distal limb anomalies, none has been reported in association with delayed intramembranous ossification. Here, we report a family of three males with apparent autosomal dominant transmission of microphthalmia and related ocular abnormalities, postaxial polydactyly, and delayed intramembranous ossification. The affected males in this family appear to have a previously undescribed syndrome of multiple anomalies consistent with autosomal dominant inheritance.

Case reports

CASE 1

A 5 month old boy was referred for evaluation of multiple congenital anomalies including skeletal and unilateral ocular anomalies. He was born weighing 4167 g at 39 weeks' gestation to a 27 year old, gravida 2, para 1 mother. His father was 32 years old. No intrauterine exposure to alcohol or other teratogens was reported. He was diagnosed in the immediate postnatal period with a markedly enlarged right globe, opacification of the cornea and lens, and bilateral postaxial polydactyly. At 1 day of age, increased anterior chamber pressure was noted, and he underwent surgery for congenital glaucoma at the age of 1 week with revision at 1 month. Repeated examinations of the left eye showed no increased pressure and no abnormalities of the lens, iris, or retina. Within the first month of life, he underwent bilateral ligation of the supernumerary digits.

Physical examination at the age of 5 months showed growth parameters on the 50th centile:

weight 7.34 kg, length 66.5 cm, and OFC 44.1 cm. Cranial examination was remarkable for a large 7 × 7 cm anterior fontanelle. The posterior fontanelle and a third fontanelle were open at 1 × 1 cm. The right globe was much larger than the left, with opacity of the right cornea and lens. Facial features were notable for a high, prominent forehead, shallow nasal bridge, downward slanting palpebral fissures, bilateral epicanthic folds, and mild micrognathia. Ear helices were slightly overfolded and prominent. No dental hypoplasia or enamel defects were noted. A left accessory nipple was present. The clavicles were normal with no hypoplasia. Examination of the extremities showed no distal digital or radial anomalies. Chromosome analysis of peripheral blood leucocytes showed a normal 46,XY karyotype. Re-evaluation at 18 months showed unchanged ocular and facial features (fig 1A). His parents were non-consanguineous; a family history of ocular and skeletal anomalies was present in his father (case 2) and brother (case 3).

CASE 2

The 31 year old father of case 1, also examined in our clinic, had a past medical history notable only for ocular and skeletal abnormalities. He was noted in infancy to have left sided scleralisation of the cornea, microphthalmia, and eccentric placement of the pupil. Ophthalmological evaluation confirmed these findings and showed left sided staphylomatous retinal coloboma and microcornea. He had a history of delayed anterior fontanelle closure in early childhood, but no palpable cranial abnormalities or persistence of the fontanelles on physical examination. Mild facial dysmorphism was present, including a prominent nasal bridge, downward slanting palpebral fissures, mild bilateral ptosis, and micrognathia (fig 1B). Dentition was normal. His ears were normally placed, with overfolded helices and a preauricular tag in the right pretragal region. The clavicles and chest were normal. A small scar at the lateral aspect of the left fifth digit was noted, consistent with surgical ligation of non-osseous postaxial polydactyly. He also had broad fingertips, prominent finger pads, and shallow nails, with no evidence of radial abnormalities or distal digital hypoplasia.

CASE 3

The proband's 2½ year old brother was born by normal vaginal birth, weighing 3884 g, at 39 weeks' gestation to a 25 year old primigravida, whose pregnancy was uncomplicated by exposure or illnesses. Postaxial polydactyly of the left hand was noted at delivery and treated by ligation. He also had left internal tibial torsion, left talipes equinovarus, and mild metatarsus adductus of the left lower extremity requiring surgical repair at 5 months, followed by immobilisation. Other medical problems developed in the first two years, including admission to hospital for bronchodilator treatment for reactive airway disease. Bilateral tympanostomy tube placement and right inguinal herniorrhaphy were performed at 15 and 17 months, respectively. At 18 months, persistence of the anterior fontanelle was noted with normal thyroid function tests. Repeated auditory examinations, growth, and development were normal.

Examination in our clinic at the age of 2½ years showed normal growth parameters on the 50th-75th centile: weight 13.5 kg, height 94.6 cm, and OFC 50 cm. His anterior fontanelle was open 2 × 2 cm, with a palpable third fontanelle. The posterior fontanelle was closed. Mild facial dysmorphism was noted, including prominence of the nasal bridge, downward slanting palpebral fissures, and bilateral epicanthic folds (fig 1C). Dentition was normal. No clavicle abnormalities were noted. He had an accessory nipple over the abdomen in the left nipple line. Examination of the extremities showed surgical scars over the lateral aspect of

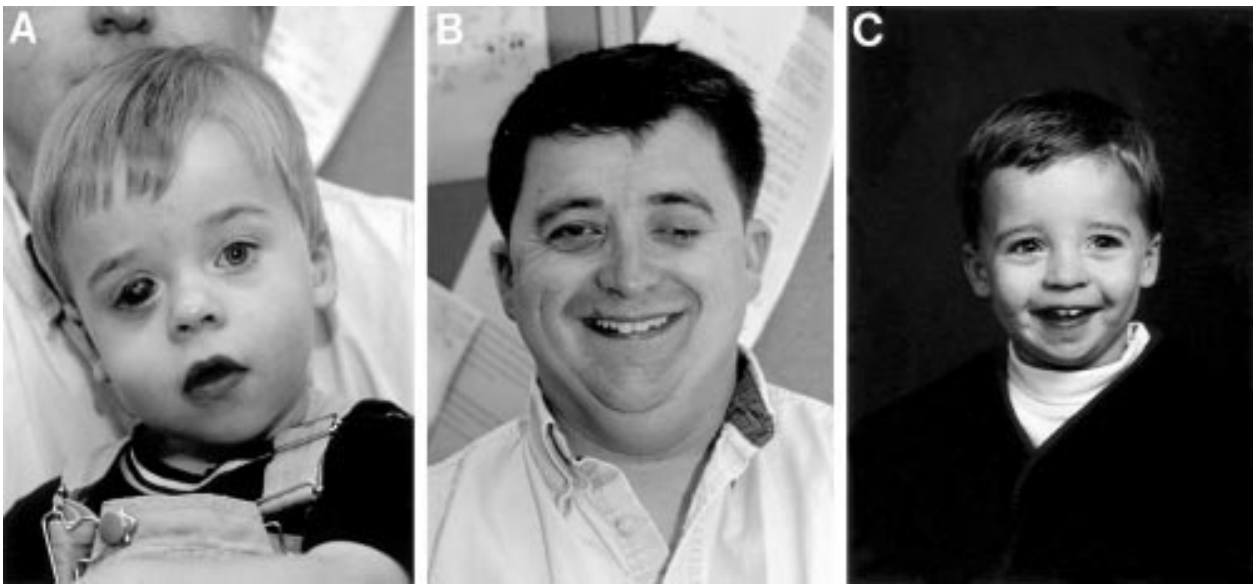

Figure 1 Photograph of (A) the proband at 18 months, showing right sided corneal clouding, downward slanting palpebral fissures, and mild micrognathia, (B) the 31 year old father, showing left corneal clouding and microphthalmia, downward slanting palpebral fissures, and mild micrognathia, and (C) the 2½ year old brother, showing facial features including downward slanting palpebral fissures and prominent nasal bridge.

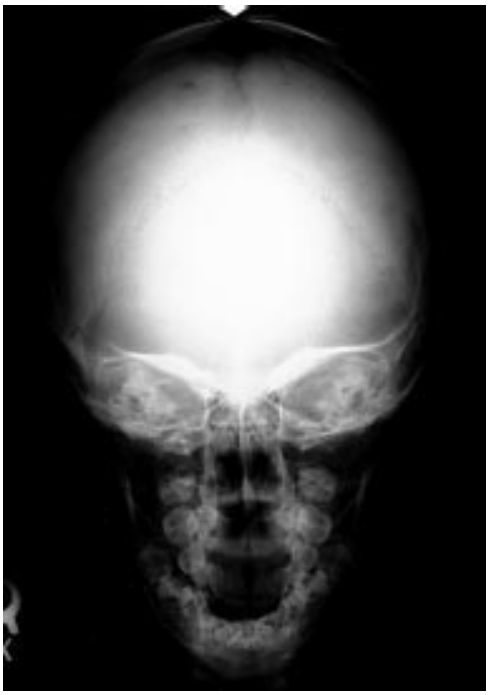

Figure 2 Skull radiograph of the 2½ year old child (case 3) showing patency of the anterior fontanelle (white arrow).

the left fifth digit at the first metacarpophalangeal joint and over the lateral aspect of the left foot. The left lower extremity exhibited marked internal tibial torsion, with mild metatarsus adductus. The fingernails were mildly short, but no digital hypoplasia or radial anomalies were present. Physical examination was otherwise normal. Skull radiograph confirmed persistence of the anterior fontanelle and no wormian bones or abnormal falcine calcification (fig 2). Skeletal survey showed no shortened or abnormally formed bony elements. The family pedigree indicated ocular and skeletal anomalies in the patient's father and 5 month old brother (fig 3). By history, no other family members were affected.

Discussion

We describe a family of three affected males with microphthalmia and related ocular abnormalities, postaxial polydactyly, delayed intramembranous ossification of the skull, minor facial dysmorphic features, and accessory nipples. Characterisation of the ocular abnormalities showed anterior and posterior ocular defects, varying from unilateral congenital glaucoma in the 5 month old boy to unilateral microcornea, retinal coloboma, and microphthalmia in the father. Skeletal abnormalities included non-osseous postaxial polydactyly of the upper extremities and delayed fontanelle closure in all three affected males, and left sided talipes equinovarus and tibial torsion in the 2½ year old boy. Growth and development were normal, and karyotype analysis showed normal chromosomes. This unique collection of features appears to be segregating in the family by male to male transmission, suggesting autosomal dominant inheritance.

The eye defects in this family include anterior segment anomalies (glaucoma and cataracts), posterior segment defects (retinal coloboma), and a combination of both (microphthalmia). Several different embryological germ layers contribute to the development of anterior and posterior ocular structures. Neural crest cells and ectoderm form the anterior chamber and lens placode, respectively, whereas neuroectoderm gives rise to the optic vesicles and, along with mesoderm, participates in optic fissure closure. The embryological heterogeneity of congenital ocular defects is thought to contribute to the wide variability in phenotype commonly seen among subjects within the same family.[4] The absence of ocular defects in the 2½ year old boy suggests incomplete penetrance, and also raises the possibility that the eye and skeletal defects may be segregating independently. It is interesting to note that both the father and his 5 month old son exhibited unilateral ocular defects. In one recent study, unilateral defects were present in 40% (52 of 131) patients with anophthalmia or microphthalmia.[5] The same study also found that bilateral and unilateral ocular malformations are similarly associated with other congenital anomalies, making laterality an unhelpful predictor of other organ system defects.

In addition to ocular defects, affected family members uniformly had upper extremity non-osseous postaxial polydactyly and the 2½ year old boy had unilateral talipes equinovarus and tibial torsion. Polydactyly is a common congenital anomaly of endochondral bone formation that occurs in isolation or with syndromes and chromosomal abnormalities. Normal karyotype studies in this family ruled out an inherited chromosomal rearrangement. A recent study of associated anomalies in 5927 subjects with polydactyly indicated that postaxial polydactyly is significantly associated with syndactyly and negatively associated with limb deficiencies and deformities. The same study

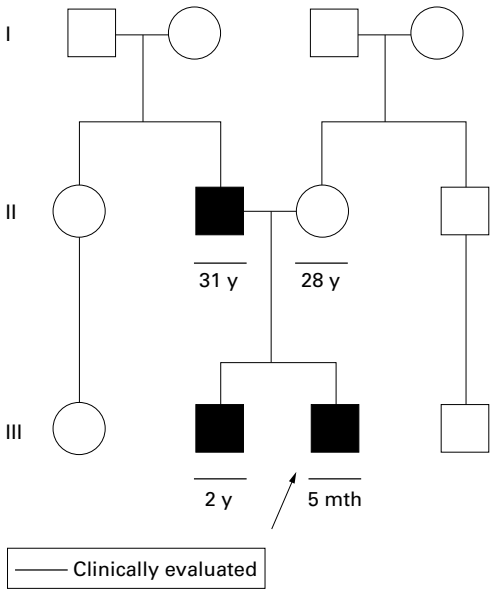

Figure 3 Three generation pedigree showing the proband (arrow) and affected and unaffected family members. Age at initial evaluation is shown.

Table 1 Comparison of autosomal dominant conditions with ocular and skeletal anomalies

Clinical features	*Present cases*	*Acroreno-ocular syndrome*[7 8]	*Macular coloboma with type B brachydactyly*[9 10]	*Oculodentodigital dysplasia*[11 12]	*Pallister-Hall syndrome*[13 14]	*Kenny-Caffey syndrome type 2*[15 16]	*Acrofacial dysostosis 1, Nager type*[17]
Microphthalmia or coloboma	2/3	+	+	+	+	Hyperopia	−
Postaxial polydactyly	2/3	−	−	−	+	−	+
Delayed intramembranous ossification	3/3	−	−	−	−	+	−
Accessory nipples	2/3	−	−	−	−	−	−
Talipes equinovarus	1/3	−	−	−	−	−	−
Thumb and radial defects	0/3	+	+	−	+	−	+
Distal phalangeal hypoplasia	0/3	+	+	+	+	−	+
Renal anomalies	0/3	+	+	−	+	−	
Other	0/3	*	†	‡	§	¶	**

*Preaxial polydactyly.
†Deafness, upper extremity 4, 5 syndactyly.
‡Preaxial polydactyly, upper extremity 4, 5 syndactyly, dental hypoplasia, spastic paraparesis, hypotelorism.
§Hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, mental retardation.
¶Hypocalcaemia, hypophosphataemia, short stature, macrocephaly, micro-orchidism.
**Distinctive facies, micrognathia.

also concluded that polydactylies are rarely associated with other congenital anomalies except in recognisable syndromes.[6]

Comparison of the clinical features present in this family showed minimal overlap with six other known genetic conditions, particularly in the type and extent of ocular and distal limb anomalies; however, each of these previously recognised conditions included other major diagnostic features not present in this family (table 1). Of the autosomal dominant conditions associated with microphthalmia or related ocular malformations and distal limb anomalies, none is reported to have delayed intramembranous ossification, a prominent finding in this family. In acroreno-ocular syndrome (OMIM 102490), distal limb defects are typically preaxial and renal abnormalities are prominent.[7 8] Apical dystrophy (OMIM 120400), or coloboma of the macula with type B brachydactyly, involves absence of the distal phalanges, different from the non-osseous polydactyly present in this family.[9 10] Although oculodentodigital dysplasia (ODD, OMIM 164200) shares several features with this family, including microphthalmia, microcornea, glaucoma, and minor postaxial digital anomalies, the typical dental abnormalities of ODD (hypoplastic enamel and small teeth) were absent in this family, and the family had features not seen in ODD, including accessory nipples and delayed intramembranous ossification.[11 12] Some cases of Pallister-Hall syndrome (PHS, OMIM 146510) have microphthalmia and postaxial polydactyly, but the major features of PHS (hypothalamic hamartoblastoma, hypopituitarism, and imperforate anus) were not present in this family.[13 14] Kenny-Caffey syndrome (OMIM 127000), characterised by dwarfism, cortical thickening of tubular bones, and transient hypocalcaemia, has been reported with delayed intramembranous ossification and hyperopia, but does not include distal limb anomalies.[15 16] The distinctive facial features and micrognathia present in acrofacial dysostosis type 1 (OMIM 154400) were absent in the family.[17]

Delayed intramembranous ossification may be clinically under-reported, since it resolves with age and often causes no serious medical problems; however, the lack of syndromic associations with this condition are striking. Delayed anterior fontanelle closure results from abnormalities in intramembranous ossification of the frontal and parietal bones of the calvaria. Delayed fontanelle closure can also, like ocular and distal limb defects, occur in isolation or as part of other conditions. Skeletal survey in the 2½ year old male showed normal mineralisation and no bony anomalies to suggest underlying metabolic disease. Delayed intramembranous ossification has been reported in one family with a familial translocation (2;3)(p15;q12).[18 19] Delayed intramembranous ossification also occurs in cleidocranial dysplasia, a dominantly inherited skeletal dysplasia characterised by hypoplastic clavicles, large fontanelles, dental anomalies, and delayed skeletal development.[20] The absence of clavicle and dental anomalies in this family makes this diagnosis unlikely.

Based on this comparison with other genetic conditions (table 1), we conclude that this family is segregating a trait that adversely

- Ocular and skeletal malformations often occur together as part of multiple anomaly syndromes.
- We present a father and two sons with a constellation of anomalies including microphthalmia and related ocular malformations, delayed intramembranous ossification, and postaxial polydactyly. Clinical evaluation showed no chromosomal rearrangements or metabolic disorders. The physical features displayed in affected family members were compared to the clinical features of known inherited conditions associated with ocular, limb, and skeletal malformations.
- The male to male transmission in this family suggests that this multiple congenital anomaly syndrome has autosomal dominant inheritance. A comparison of the clinical features segregating in this family to features comprising autosomal dominant conditions affecting the eye and distal limb strongly suggests that this family is segregating a newly recognised condition.

affects both ocular and skeletal development, with delayed intramembranous ossification and abnormal postaxial endochondral bone formation. The observed male to male transmission strongly suggests autosomal dominant inheritance. While there is some overlap of these features with previously reported genetic conditions, none exhibits delay in intramembranous ossification and most involve other organ systems unaffected in this family. This constellation of clinical findings represents a unique condition and suggests a distinctive autosomal dominantly inherited syndrome. Identification of other similarly affected subjects may eventually shed light on underlying causative mechanisms and broaden our understanding of ocular and skeletal development.

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Recessively inherited lower incisor hypodontia

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EDITOR—Hypodontia, congenitally missing teeth, is common in modern man. The teeth most often missing in populations of European origin are the upper lateral incisors and second premolars. The condition is known to have a strong genetic component. At present two mutated genes in humans, *MSX1*[1] and *PAX9*,[2] are known to cause missing permanent teeth. Mutations in *MSX1* can also cause orofacial clefting.[3] Several experimental and clinical studies indicate that other genetic components are also involved.[4–8] Hypodontia is also often seen in syndromes, particularly in those which present with other ectodermal anomalies,[9] and in non-syndromic patients with cleft lip/alveolus with or without cleft palate.

The population prevalence of the common incisor-premolar hypodontia (IPH, MIM 106600) is 8-10% in healthy European children. Some or all third molar teeth are missing in one-fifth of the population,[10] and missing third molars are seen in varying combinations in IPH patients and/or family members.[11] Family studies also indicate that peg shaped upper lateral incisors, impacted canines, rotated bicuspids, and short root anomaly (SRA) are caused by the same genetic components that cause missing incisors and premolars.[12–15] The condition is inherited as an autosomal dominant trait[16] with reduced penetrance and is mostly restricted to the permanent dentition. When a large number of teeth (>6) are congenitally missing, the term used is oligodontia (MIM 6044625). The prevalence of oligodontia in European populations is estimated at 0.08%,[17] but this figure also includes syndromic patients.

We describe 37 Finnish patients from 34 families with several lower incisors and upper lateral permanent incisors congenitally missing. In half of the patients, the corresponding deciduous teeth had either been missing or peg